Remittance of primary cutaneous CD30$^+$ lymphoproliferative disorder in a patient on adalimumab

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INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic intestinal inflammation of unknown etiology. It is associated with significant morbidity and high burden of hospitalization.[1] The prevalence of IBD has been increasing recently. This has resulted in an increase in the prescription of anti-tumor necrosis factor-alpha (anti-TNF-α) agents or other immunomodulatory therapies.[2] Recent studies have highlighted that patients with IBD receiving anti-TNF-α agents or other immunomodulatory therapies might have an increased risk of developing cutaneous T-cell lymphomas.[3] Indeed, isolated cases of patients who developed a CD30$^+$ lymphoproliferative disorder after the use of anti-TNF-α agents have been described.[4,5]

Primary cutaneous CD30 + lymphoproliferative disorders (pcCD30$^+$ LPDs) form a spectrum of cutaneous anaplastic large cell lymphoma (C-ALCL) on one side, lymphomatoid papulosis (LyP) on the other, and borderline cases in between. These pcCD30$^+$ LPDs account for approximately 30% of all cutaneous T-cell lymphomas. We report of a patient with Crohn's disease and a persisting, therapy-resistant pcCD30$^+$ LPD borderline case who had an unexpectedly favorable clinical course after treatment with the anti-TNF-α agent adalimumab.

Abbreviations used:

C-ALCL:	cutaneous anaplastic large cell lymphoma
CD:	Crohn's disease
IBD:	inflammatory bowel disease
LyP:	lymphomatoid papulosis
NF-kB:	Nuclear factor kappa-light-chain-enhancer of activated B cells
pcCD30$^+$ LPD(s):	primary cutaneous CD30-positive lymphoproliferative disorder(s)
TNF:	tumor necrosis factor

CASE REPORT

A 74-year-old man with a 10-year history of pcCD30$^+$ LPD was followed regularly in our outpatient cutaneous lymphoma clinic. In addition, he had a history of active Crohn's disease (CD) of more than 30 years, for which he underwent a bowel resection early in his disease course. He was currently receiving 5-aminosalicyclic acid for CD without adequate control. The medical history otherwise was not contributory. Over time, he had lesions on the left (and, to a lesser extent right) leg characterized by both self-resolving papules with waxing and waning course and persistent ulcerative tumors (Fig 1). Biopsies consistently demonstrated pcCD30$^+$ LPD, in line with borderline pcCD30$^+$ LPD given overlapping clinical features of LyP and C-ALCL (Fig 2). No extracutaneous/systemic involvement was present on a computed tomography scan, when the patient first developed the ulcerative tumors. The pcCD30$^+$ LPD was treated with topical and intralesional corticosteroids, local radiotherapy, total leg irradiation (10 × 2 Gy) and methotrexate (10 mg for 2 months), all with only partial responses (Fig 3).

Meanwhile, the general condition of the patient declined due to a flare of his CD. Due to the previous side effects of methotrexate (severe fatigue, nausea, and pulmonary symptoms), after

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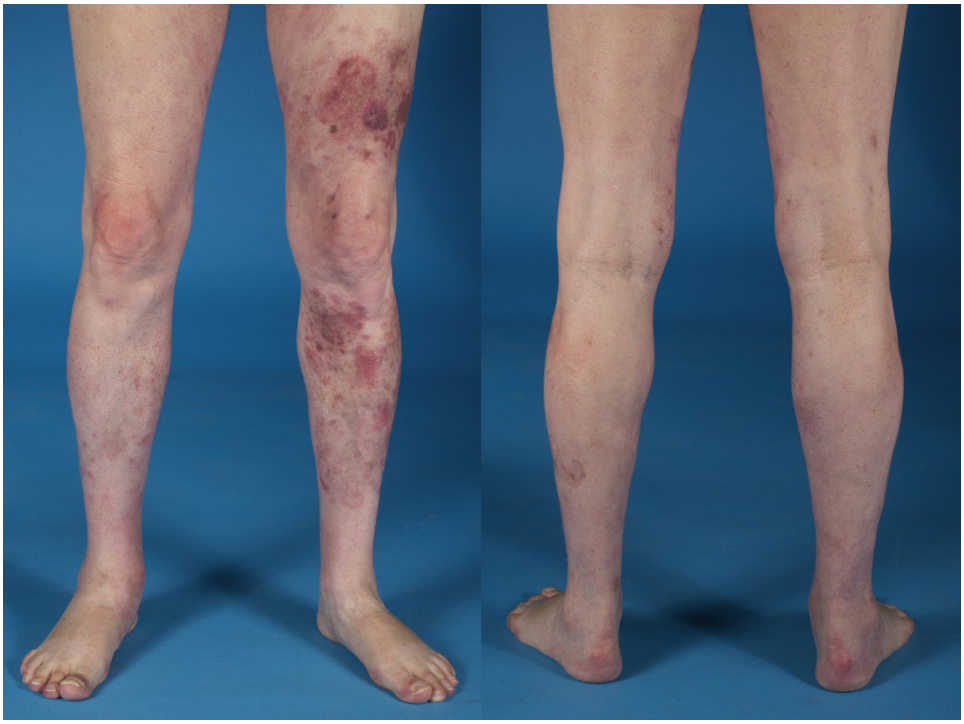

Fig 1. Persistent primary cutaneous CD30$^+$ lymphoproliferative disorder (pcCD30$^+$ LPD) lesions on the left leg before treatment with adalimumab.

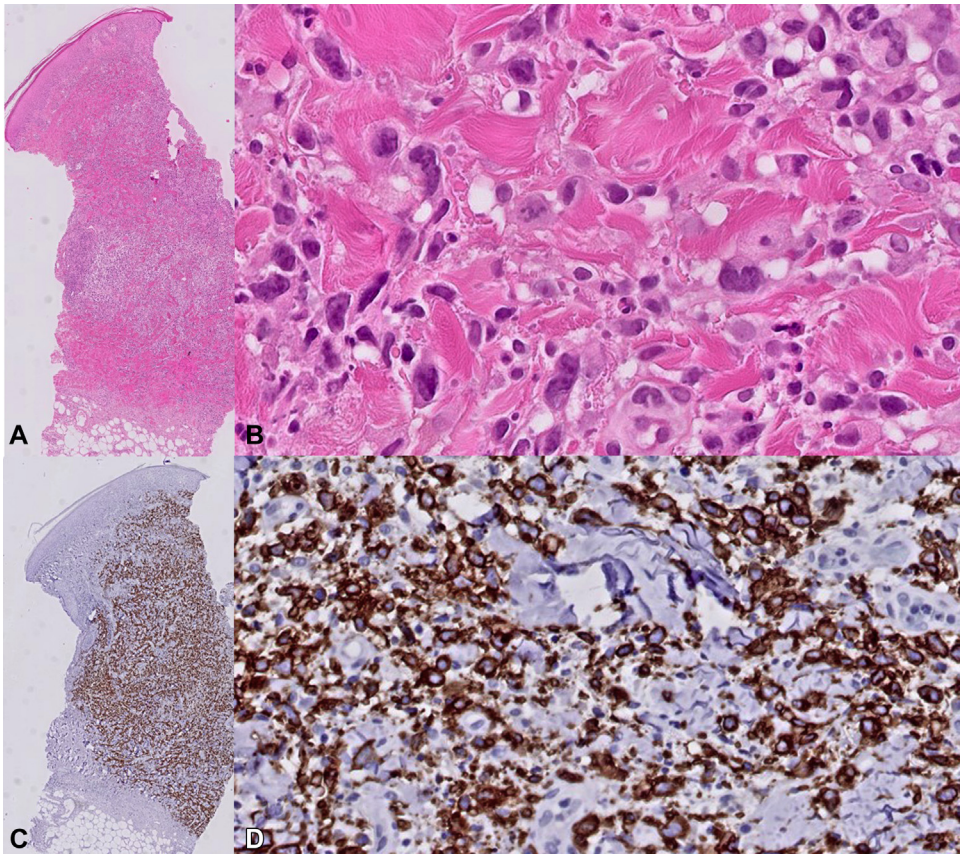

Fig 2. A, Biopsy overview showing a dense dermal infiltrate of atypical lymphocytes (hematoxylin-eosin stain; original magnifications: **A** and **C**: ×2). **B,** Details of large atypical cells (hematoxylin-eosin stain; original magnifications: **B** and **D**: ×60). **C,** Overview of CD30$^+$ of abnormal lymphoid cells in the dermis. **D,** Details of CD30 expression of atypic lymphocytes consistent with primary cutaneous CD30$^+$ lymphoproliferative disorder (pcCD30$^+$ LPD).

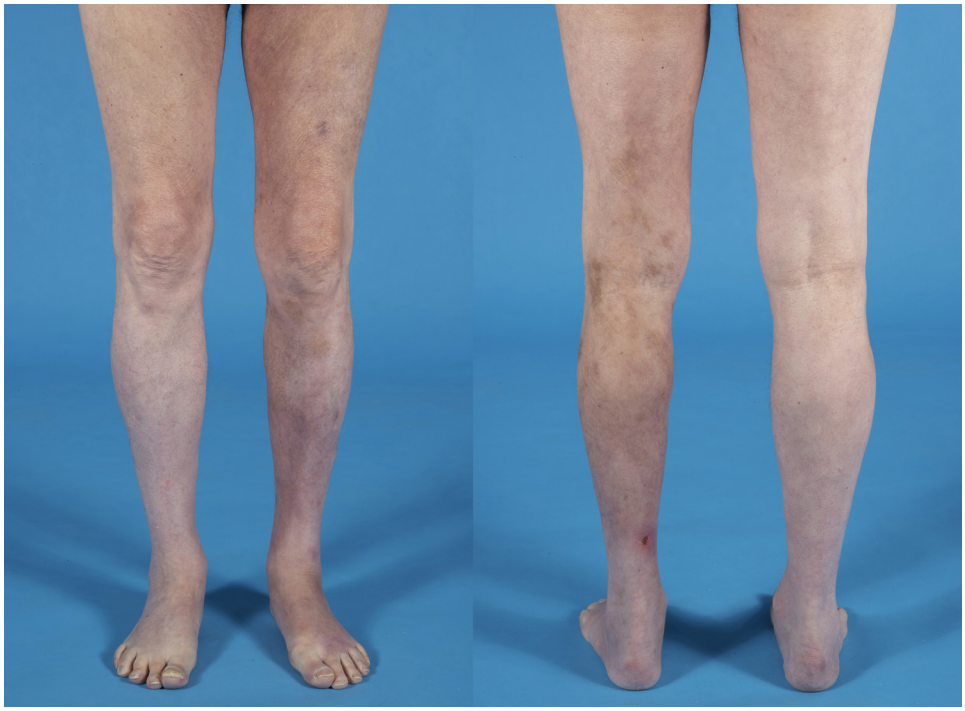

Fig 3. Complete remission of the primary cutaneous $CD30^+$ lymphoproliferative disorder ($pcCD30^+$ LPD) lesions on the left leg 4 months after the start of adalimumab therapy.

careful consideration, the patient was prescribed an anti-TNF-α agent (adalimumab) with a loading dose and a weekly dose of 40 mg. Remarkably, within 4 months of adalimumab therapy, the patient showed complete remission of the C-ALCL and LyP lesions on his left leg (Fig 2). There was a partial response of his CD.

DISCUSSION

Patients with C-ALCL present with persisting solitary or localized tumors, histologically characterized by large cells with anaplastic cytomorphology and expression of the CD30 antigen by more than 75% of the tumor cells. LyP is defined as a chronic, recurrent, self-healing (waxing and waning) papulonecrotic or papulonodular skin disease with histologic features suggestive of a ($CD30^+$) malignant lymphoma.

Because of the overlapping histologic and phenotypic features, clinical presentation and clinical course are used as decisive criteria to differentiate between LyP and C-ALCL and to select the appropriate type of treatment.[6,7] The term 'borderline cases' refers to cases in which a definite distinction between C-ALCL and LyP cannot yet be made.

Both C-ALCL and LyP have an excellent prognosis, with C-ALCL having a 10-year disease-specific survival of 90% and LyP almost 100%. Only a very small proportion of patients develop extracutaneous disease and require systemic treatment during the course of their disease.[6,7]

Lymphomas are more frequently observed in patients with IBD.[3] This association might be due to chronic inflammation or the prolonged use of immunosuppressive medication.

This is a remarkable case of a positive effect of adalimumab in a patient with IBD and cutaneous lymphoma on both the CD and the C-ALCL. In this case, the patient experienced complete remission of the skin lesions of his partially refractory C-ALCL for the first time in 10 years. This is remarkable, since a rare response to anti-TNF-α agents is the development of lymphoma, and therefore anti-TNF-α agents for chronic inflammatory disease or IBD are discouraged for patients with cutaneous lymphoma. In addition, the few cases of cutaneous lymphoma that have been reported in the literature were characterized by their sudden onset and rapid progression after treatment with adalimumab.[8] However, conflicting evidence remains on this topic, as studies lack statistical power to quantify the incidence of a very rare disease as a consequence of a rare exposure, and some studies do not support the association of an increased risk of lymphomas after adalimumab.[9]

Since the CD30 and TNF-α receptors are both cell surface receptors that interact indirectly with each other and activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway, leading, in the case of lymphoma, to uncontrolled proliferation. Ligation of CD30 by

CD30 inhibitors results in cell apoptosis by blocking the NF-kB pathway activation. In our case of a patient with pcCD30$^+$ LPD, the TNF-α inhibitor resulted in complete remission of the skin lesions. We hypothesize that inhibition of TNF-α by adalimumab might also stop the NF-kB pathway activation, which consequently results in cell apoptosis and clinical clearing of the CD30$^+$ lesions. Potentially, this could mean that TNF-α inhibitors could be used as a novel treatment for pcCD30$^+$ LPD. Nevertheless, this hypothesis has to be further investigated/elucidated in more extensive studies to determine the appropriate treatment and recommendations of TNF-α inhibitors in the setting of pcCD30$^+$ LPDs.[10]

Conflicts of interest

None disclosed.

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